Remarks

Applicants have canceled claims 26-29 and 39-47 herein without prejudice or disclaimer. Applicants reserve the right to pursue subject matter encompassed by all canceled claims in one or more divisional or continuation applications. Applicants have amended claim 25 to further define the claimed embodiments of the invention. Support for amendments to the claims made herein can be found throughout the specification as filed. Thus, no new matter has been added. Upon entry of this amendment, claims 25, 30-38, and 48 will be pending. Claim 48 is currently withdrawn.

I. Rejection of the Claims Under 35 USC § 101/112

Claims 25-47 stand rejected under 35 USC §§ 101 & 112, first paragraph for allegedly lacking a patentable utility. *See*, pages 2-4 of Paper No. 20060906. Although the Examiner has noted the arguments made and referenced cited by the Applicant to support the utility of the claimed invention, the Examiner has maintained the utility rejection, claiming that HFXHC41 is still uncharacterized and the references do not provide evidence of biological activity. Applicants respectfully disagree and traverse.

As an initial matter, Applicants point out that "an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101." M.P.E.P. § 2107.02(III)(A); *see also*, In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong,' even where there may be reason to believe the assertion is not entirely accurate." M.P.E.P. § 2107.02(III)(B). "Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made." M.P.E.P. § 2107.02. Further, the PTO must accept the manner of making and using an invention disclosed in a specification "unless there is a reason for one of skill in the art to question the objective truth of the statement of utility or its scope." In re Langer, 183 U.S.P.Q. at 297; *see also, In re* Marzocchi, 58 C.C.P.A. 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) *and Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1098-99 (Jan. 5, 2001). Indeed, the Federal Circuit has characterized the standard for utility by indicating:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson*, 383 U.S. 519, 534 (1996); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 247, 275 (7th Cir. 1903) (the test for utility is whether the invention "is capable of serving any beneficial end").

Juicy Whip, Inc. v. Orange Bang Inc., 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999).

Accordingly, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility. *See,* M.P.E.P. § 2107; *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995); and, *In re* Cortright, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). The Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *See id.* Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, if Applicants have presented reasoning used in asserting a utility, the Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Applicants' assertion of utility. *See id.* For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

The Examiner continues to discount the asserted utilities of HFXHC41 as not credible, contending that there is no proof that HFXHC41 exhibits the biological functions that have been asserted. Applicants respectfully submit that the Examiner is applying the wrong standard. As detailed above, the burden is on the Examiner to provide evidence to show that the asserted utilities would be considered false. The specification as filed teaches that HFXHC41 contains two link domains. A link domain is defined as "a hyaluronan(HA)-binding region found in proteins of vertebrates that are involved in the assembly of extracellular matrix, cell adhesion, and migration" *See*, Specification, page 14, paragraph [0041]. Furthermore, the specification teaches that HFXHC41 is "expressed primarily in adult brain, multiple sclerosis, Human Manic Depression Tissue, Spinal Cord, Hippocampus, Substantia Nigra, frontal cortex, and to a lesser extent, in placenta." *See* page 16, paragraph [0045]. The specification teaches that "elevated

expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival." *See*, page 17, paragraph [0048]. Accordingly, the specification teaches that the compositions of the claimed invention "are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions." More specifically, the specification states, "the uses include, but are not limited to the detection, treatment, and/or prevention of... schizophrenia." *See*, pages 17-18, paragraph [0048]. It was well known that the time of filing that HA and HA-binding proteins are important in forming the extracellular matrix of the brain and that the extracellular matrix is neurotrophic and affects neurite outgrowth. *See*, Exhibit A. Accordingly, Applicants submit that a person of ordinary skill in the art would not have doubted the asserted utilities of HFXHC41 at the time the specification was filed. Additionally, the Examiner has not provided the Applicants with any evidence that a person of ordinary skill in the art would believe the asserted utilities are false.

Although the Examiner did not provide the Applicants with a *prima facie* showing as required by the M.P.E.P., Applicants provided the Examiner with post filing date publications to further support the asserted utilities of HFXHC41 as first described in the instant application. In the final Office Action, the Examiner states that "[a]lthough HFXHC41 encodes for the two link domains, the other part of the polypeptide has not been characterized. It may be that this part prevents HFXHC41 binding to HA or interacts with a protein that prevents it from binding to HA." As previously submitted by the Applicant, Oohashi *et al.* teaches that HFXHC41 does indeed bind to HA. *See*, Oohashi *et al.*, pages 49-50, entitled "Brall Is a Hyaluronan-Binding Protein". In this section, the authors describe a HA binding assay, with appropriate controls, which clearly demonstrates that HFXHC41 binds to HA. Oohashi *et al.* concludes that "[t]he characteristic accumulation of Brall on axons at the nodes of Ranvier indicates that Brall may play a pivotal role in the HA-associated matrix for neuronal conduction in the mature CNS." *See*, Oohashi *et al.*, page 52, right column, first full paragraph.

Furthermore, Nomoto *et al.* report that, "[t]he brain- and nerve-tissue specificity displayed by *BRAL1* and *BCAN* marks its abnormal form as a potential candidate for involvement in neurological diseases." *See*, page 27, right column, third paragraph. The authors further describe the identification of repetitive CA repeats within the BRAL1 and BCAN genes

and provides analysis of polymorphisms in the identified regions, concluding, "[t]he highly informative CA-repeat marker HNCA2 presented here would facilitate the investigation of the possibility that BRAL1 and BCAN genes may be involved in inherited schizophrenia." *See*, page 29, last sentence. Clearly, as indicated by the above references, one of ordinary skill in the art would not consider the asserted utilities false. On the contrary, the above cited references provide no evidence that contradicts the asserted utilities of HFXHC41 as originally filed in the instant specification.

In view of the above, Applicants respectfully submit that the presently claimed invention possesses specific, substantial, credible utilities which constitute patentable utilities under 35 USC § 101. Thus, even assuming, *arguendo*, the Examiner had established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by sufficient evidence to lead one skilled in the art to conclude that at least one of the asserted utilities is more likely than not specific, substantial, and credible. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Examiner has further rejected claims 24-47 under 35 U.S.C. § 112, first paragraph, alleging that one skilled in the art clearly would not know how to use the claimed invention since the claimed invention is not supported by either a specific, substantial, credible utility, asserted utility or a well established utility. In view of the arguments presented above in response to the rejection under 35 USC § 101, Applicants submit that the claims are supported by a specific, substantial, and credible asserted utility, and thus adequately teach how to use the invention. Accordingly, it is requested that the instant rejection be reconsidered and withdrawn.

II. Rejection Under 35 USC § 112, First Paragraph

Claims 25, 27-38 stand rejected under 35 USC §112, first paragraph for allegedly lacking written description. This is a new matter rejection. Specifically, the Examiner states that, "[a]lthough Applicants have indicated that several parts of the specification that can provide support for the new matter, they do not provide specific support for an antibody binding at least 30 or 50 contiguous amino acid residues specific for SEQ ID NO:48."

Applicants respectfully disagree. In the previous response, Applicants pointed to numerous passages in the specification that provide specific support for an antibody binding at least 30 or 50 contiguous amino acid residues of SEQ ID NO:48. However, solely to facilitate

allowance of the application, claim 25 has been amended herein to obviate the rejection. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks and amendments be entered and made of record in the file history of the instant application. In view of the foregoing remarks, Applicants believe that this application is now in condition for further examination. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: Dec. 18, 2006

Respectfully submitted,

By _____

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EXHIBIT A

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MINI REVIEW

Brain extracellular matrix

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The extracellular matrix of the adult brain tissue has a unique composition. The striking feature of this matrix is the prominence of lecticans, proteoglycans that contain a lectin domain and a hyaluronic acid-binding domain. Hyaluronic acid and tenascin family adhesive/anti-adhesive proteins are also abundant. Matrix proteins common in other tissues are nearly absent in adult brain. The brain extracellular matrix appears to have trophic effects on neuronal cells and affect neurite outgrowth. The unique composition of this matrix may be responsible for the resistance of brain tissue toward invasion by tumors of non-neuronal origin.

Key words: extracellular matrix/lectican/versican/review

Introduction

A large proportion of the brain volume is thought to consist of space filled with extracellular matrix (ECM) (Rutka *et al.*, 1988), yet electron microscopy and immunostaining show relatively low content of fibrous matrix proteins such as collagens, fibronectin and vitronectin (Rutka *et al.*, 1988; Rucklidge *et al.*, 1989; Stallcup *et al.*, 1989; Asher *et al.*, 1991; Gladson and Cheresh, 1991), or basement membrane proteins, such as laminin (Hägg *et al.*, 1989). The heparan sulfate proteoglycan perlecan is only present in amyloid deposits of the brain (Snow *et al.*, 1994). Some of these ECM components are present in the embryonic brain; the various forms of laminin, in particular, are thought to play a major role in nervous tissue development as guidance molecules for nerve cell processes (Rutka *et al.*, 1988). As development is completed these matrix components are down-regulated to levels where they can be detected only with some difficulty by immunostaining and only in certain parts of the brain. Although quantitative studies have not been conducted, it appears that the brain ECM may primarily consist of a family of proteoglycans, which I propose to name lecticans, and two ECM components to which they bind, tenascins and hyaluronic acid.

Lectican family of proteoglycans in brain

Proteoglycans are important components of cell surfaces and ECMs, including those of the brain; they can regulate cell adhesion, neurite outgrowth, ECM assembly and tumor cell invasion (Ruoslahti, 1989), and they also serve as cofactors and regulators of growth factors (Ruoslahti and Yamaguchi, 1991). Of the several families of proteoglycans, members of the lectican family of proteoglycans appear to be particularly abundant in brain tissue.

Four members of the lectican family have been cloned: versican (Zimmermann and Ruoslahti, 1989), aggrecan (Doege *et al.*, 1991) neurocan (Rauch *et al.*, 1992) and brevican (Yamada *et al.*, 1994). Like all proteoglycans, lecticans consist of a core protein and a glycosaminoglycan moiety. The lectican core proteins are large, ranging from 80 to 400 kDa in molecular weight. Their sequences are highly homologous, but all four are clearly products of distinct genes. The core proteins display an N-terminal hyaluronic acid-binding domain that is homologous to the cartilage link protein and to the homing receptor CD44 and a C-terminal domain comprised of EGF-like repeats, a C-type lectin motif and complement regulatory protein repeats (Figure 1). These are the same structural units, albeit in a different order, as the ones that make up the carbohydrate-binding adhesion receptors, selectins (Lasky, 1992). The middle portion of the core proteins contains attachment sites for glycosaminoglycan chains, which are of the chondroitin sulfate variety. The length and structure of this part varies greatly among the members of the family. In addition, alternative splicings create variants of the individual lecticans (Dours- Zimmermann and Zimmermann, 1994).

Versican is abundant in the brain, but is also expressed in many other tissues (Krusius *et al.*, 1987; Schönherr *et al.*, 1991; LeBaron *et al.*, 1992; Bignami *et al.*, 1993). Neurocan was identified in brain tissue; its mRNA is not detectable in several other tissues (Rauch *et al.*, 1991, 1992). Brevican appears to be specifically expressed in the brain (Yamada *et al.*, 1994). Aggrecan is a proteoglycan characteristic of cartilage (Hascall, 1988), but immunological data (see Hennig *et al.*, 1993) and the presence of aggrecan cDNA clones in a brain cDNA library (E. Ruoslahti and S. Suzuki, unpublished data) suggest that aggrecan may also be expressed in brain tissue. In addition to the proteoglycan form, brain tissue also contains versican and brevican core proteins that lack the glycosaminoglycan (Bignami *et al.*, 1993; Yamada *et al.*, 1994). Proteins known as glial hyaluronic acid-binding protein (Perides *et al.*, 1992) and hyaluronectin (Delpech *et al.*, 1989) appear to represent free N-terminal domains of versican and perhaps of one of the other members of the family.

Several additional large chondroitin sulfate proteoglycans that may also be members of the lectican family have been identified in brain tissue. These include Cat 301 (Fryer *et al.*, 1992), Ti antigen (Iwata and Carlson, 1993) and astrochondrin (Streit *et al.*, 1993), and there may be others (Herndon and Lander, 1990; Rauch *et al.*, 1991). The core proteins of these proteoglycans have not been cloned yet, so their relationship to the more fully characterized proteoglycans remains unclear. However, their expression patterns and some other properties suggest that these proteoglycans may not be identical to any of the four cloned members of the lectican family. Thus, the lectican family of hyaluronic acid-binding proteoglycans is a

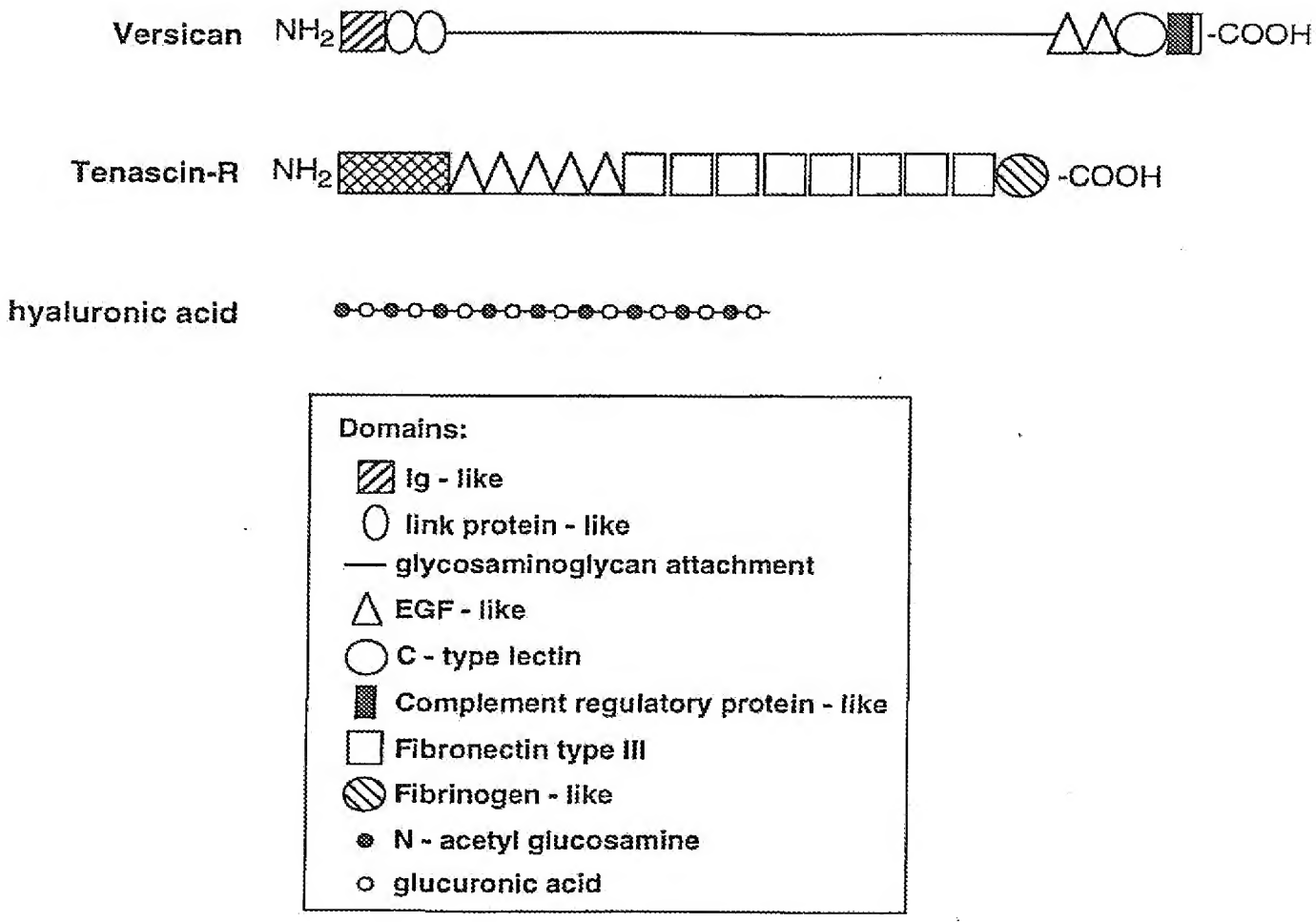

Fig. 1. General structures of a lectican (Versican), a tenascin (Tenascin-R) and hyaluronic acid.

large one, and it also appears that at least four of the members of this family are preferentially expressed in central nervous tissue.

Lectican binding functions

What might be the significance of the predominance of lecticans in the central nervous tissue? The hyaluronic acid-binding property of lecticans is likely to be important in this regard. The addition of aggrecan to a hyaluronic acid-producing cell culture results in the formation of an organized hyaluronic acid-proteoglycan coat around the cells (Knudson, 1993). Thus, the lecticans seem to play a role in the organization of a hyaluronic acid-proteoglycan ECM. *In vivo* this matrix contains link protein (Meyer-Puttlitz *et al.*, 1995), a 45 kDa protein that reinforces the interaction between hyaluronic acid and a proteoglycan.

The matrices containing different lecticans may be quite different in some of their properties, because lecticans vary greatly in length and in glycosaminoglycan content. Aggrecan, at least in the cartilage, carries as many as 100 chondroitin sulfate chains (Hascall, 1988), whereas brain tissue versican contains only a few short chondroitin sulfate chains (Perides *et al.*, 1992). Moreover, both versican and brevican exist in the brain also in a form that is devoid of glycosaminoglycan (Bignami *et al.*, 1993; Yamada *et al.*, 1994). Thus, depending on the nature of the lectican, a hyaluronic acid-proteoglycan complex can have a very different chondroitin sulfate content.

The selectin-type C-terminus of lecticans provides these proteoglycans with an additional recognition domain. The C-type lectin of this domain can bind simple sugars; this has been shown for aggrecan (Halberg *et al.*, 1988) and versican (Ujita *et al.*, 1994; Aspberg *et al.*, 1995). The target sugars for the lectins may be cell surface carbohydrates, as is the case with the selectins (Varki, 1994). However, more significant may be the recently discovered interaction of the versican lectin domain with tenascin-R (see below).

Versican-tenascin interaction

The versican lectin, isolated as a recombinantly made 15 kDa protein, binds insolubilized fucose and *N*-acetylglucosamine. As is characteristic of C-type lectins, this binding is calcium-dependent. The lectin also recognizes in a calcium-dependent manner the ECM protein tenascin-R, both in gel blots and in solution (Aspberg *et al.*, 1995). Tenascin-R and versican have

partially overlapping distributions in the brain; tenascin-R is particularly abundant in the granular layer of the cerebellum (Fuss *et al.*, 1993), and versican is seen at this same location. The versican lectin does not bind tenascin-C, which is closely related to tenascin-R. Instead, tenascin-C may be bound by neurocan (Hoffman *et al.*, 1988; Grumet *et al.*, 1994), raising the exciting possibility that the individual lecticans may each interact with a distinct tenascin; there are two additional known members in the tenascin family (reviewed in Chiquet-Ehrisman *et al.*, 1994). Versican and brevican are produced by glial cells (Bignami *et al.*, 1993; Yamada *et al.*, 1994; R. Lebaron and E. Ruoslahti, unpublished data), while neurocan appears to be made by neurons (Margolis and Margolis, 1994). However, Cat 301 is associated with surfaces of neurons (Fryer *et al.*, 1992). Cell-type specificities and distinct lectin specificities of the individual lecticans could form the basis of a recognition system similar to that constituted by the selectin family.

Lectican-assembled matrices: possible functions

Lectican interactions such as that of versican with tenascin-R, may result in the formation of unique matrices consisting of a lectican, a tenascin, and hyaluronic acid. Brain tissue appears to be rich in such matrices and, unlike other tissues that contain lecticans, the brain has little other matrix.

The chondroitin sulfate in proteoglycans has been found to be neurotrophic and can promote neurite outgrowth of some brain neurons (Faissner *et al.*, 1994; Junghans *et al.*, 1995), and inhibit it in others (Milev *et al.*, 1994; Don and Levine, 1995), thus potentially regulating neuronal patterning (Brittis *et al.*, 1992). The abundance of lecticans in the central nervous system should make their chodroitin sulfate an important contributor to such trophic and regulatory activities.

The ECM of cartilage resembles that of the brain; it is rich in aggrecan and in hyaluronic acid, but unlike the brain matrix, contains abundant fibrous collagen. The aggrecan-hyaluronic acid complex appears to serve as a cushion in cartilage (Hascall, 1988). These complexes bind a large quantity of water that is extruded when the cartilage is compressed and that returns when the compression is released. The brain may need a similar buffer against pressure, because it is confined within the skull. In this case the water released by the proteoglycan complexes could perhaps be transferred into the circulation. There

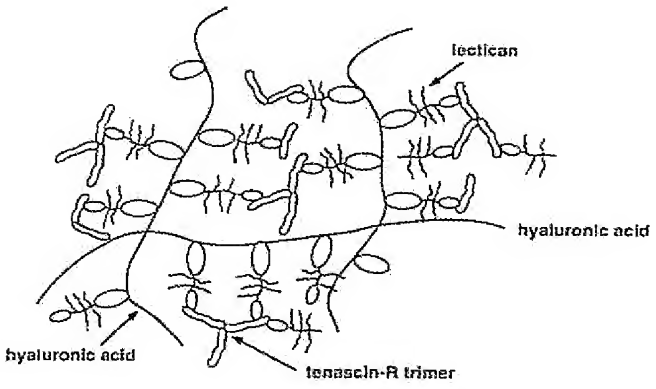

Fig. 2. A model for lectican-tenascin-hyaluronic acid matrix. Tenascin is shown as trimers, dimers and monomers, as has been shown for tenascin-R (Nörenberg *et al.*, 1992).

is one other striking parallel between cartilage and central nervous tissues: tumors rarely invade these tissues.

The resistance of the cartilage to tumor invasion has been attributed to inhibition of angiogenesis (e.g., Moses *et al.*, 1992), but other explanations seem possible. It is well known that tumors metastasize into the brain from other tissues. However, brain tissue, especially the white matter, tends to be resistant to tumor invasion (Paganetti *et al.*, 1988). In contrast, glial cell tumors, which arise in the central nervous system, readily invade brain tissue, as do early glial precursors (Paganetti *et al.*, 1988; Espinosa de los Monteros *et al.*, 1993). Interestingly, gliomas rarely metastasize outside the brain (Russel and Rubinstein, 1977), suggesting a specialization into the invasion of brain tissue. It may be the uniqueness of extracellular matrix that makes the central nervous system resistant to tumor cell invasion. Moreover, only glial cells may possess the mechanisms necessary to circumvent this resistance.

Chondroitin sulfate proteoglycans have been proposed as regulators of the growth of neuronal processes, and they may affect similarly other migration events in nervous tissues (e.g., Oakley and Tosney, 1991; Brittis *et al.*, 1992). Proteoglycans can inhibit the cell attachment activity of other matrix proteins (Ruoslahti, 1989). Cells need traction from attachment to a substrate to migrate. One possibility is that the matrices dominated by lecticans provide insufficient traction for migrating cells. Alternatively, since lecticans are capable of binding to other molecules through their lectin domain, these lectican-bound molecules, such as tenascins, could generate signals that are inhibitory for nonneuronal cell migration. Thus, the distinct properties of the lectican-tenascin-hyaluronic acid matrices (Figure 2) may underlie some of the physical and biological properties characteristic of brain tissue; this unique ECM deserves further study.

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